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Concomitant presentation of lung dominant anti-PL-7 positive anti-synthetase syndrome in association with high risk myelodysplastic syndrome

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AC - First author, wrote case outline, wrote final version of article

RP - Contributed to section on myelodysplastic syndrome, reviewed and edited final version of text

HG - Contributed to section on antisynthetase syndrome/connective tissue disease-associated ILD, reviewed and edited final version of text

SB - Wrote section on assessment of ILD (under her name in the text), reviewed and edited final version of text. Responsible for the overall content as guarantor.

Concomitant presentation of lung dominant anti-PL-7 positive anti-synthetase syndrome in association with high risk myelodysplastic syndrome

Dr Andrew Creamer, Respiratory Registrar

A seventy-year-old retired teacher was referred to the respiratory clinic with a 12-month history of progressive exertional dyspnoea and dry cough. He denied haemoptysis, constitutional symptoms or diurnal variation. He took omeprazole, amlodipine and ezetimibe for a longstanding history of dyspepsia, hypertension and hypercholesterolaemia. He was an ex-smoker with a 30-pack year history.

He reported monophasic colour change in his fingers in the cold, but denied any other connective tissue disease (CTD) symptoms. He denied any significant environmental exposures such as organic dusts or moulds.

Vital signs were normal. There was evidence of mechanic's hands (a hyperkeratotic eruption with fissuring and cracking on the palmar and radial aspect of the fingers, strongly associated with idiopathic inflammatory myopathies) but no other features of CTD or clubbing. Bibasal fine inspiratory crepitations were audible on chest auscultation. Cardiovascular examination was normal.

Initial investigations revealed a pancytopenia (Figure 1) with unremarkable liver and renal function, prompting referral to local haematology services for further assessment.

Lung function testing revealed a restrictive pattern with significantly reduced gas transfer (Figure 2), whilst 6-minute walk test demonstrated baseline saturations of 95% on air dropping to 77% on exertion, achieving 260m (48% of theoretical distance).

Chest x-ray showed prominent interstitial lung markings in the mid- and lower zones (Figure 3). High-Resolution CT Thorax (HRCT) demonstrated centrilobular emphysema throughout the lungs and a basally predominant interstitial process with features suggestive of non-specific interstitial pneumonia (NSIP) (Figure 4). Transthoracic echocardiogram showed preserved LV systolic function with mild concentric hypertrophy, normal RV size and function. There was no tricuspid regurgitation so an estimate of the pulmonary artery pressure could not be made.

Dr Shaney L Barratt, Respiratory Consultant

The differential diagnosis for interstitial lung disease (ILD) presenting in a 70-year old is broad and includes hypersensitivity pneumonitis, drug-induced ILD, CTD-ILD and the idiopathic interstitial pneumonias, particularly idiopathic pulmonary fibrosis. There was no history of pneumotoxic medication, and no relevant occupational exposures. The radiological pattern and absence of relevant exposures made hypersensitivity pneumonitis less likely. The presence of mechanics' hands in a patient with an NSIP pattern suggests the possibility of an underlying connective tissue disease and an autoimmune screen is an important part of the initial assessment of new ILD patients.

The combination of pancytopenia with ILD should prompt consideration of a short telomere syndrome, particularly if there is a family history of pulmonary fibrosis or bone marrow failure. These are a heterogeneous group of inherited disorders of variable penetrance caused by mutations that interfere with the normal maintenance of telomeres. However, the patients' age, absence of family history and lack of typical skin or systemic features would not support this.

Given the wide differential and thorough diagnostic work-up required, a multidisciplinary team (MDT) diagnosis taking into consideration clinical, radiological, histopathological and serological features is essential.

AC

Indirect immunofluorescence using HEp-2 cells demonstrated a cytoplasmic speckled pattern with no nuclear staining (anti-nuclear antibody negative / anti-cytoplasmic antibody positive). Subsequent myositis spectrum antibody immunoblot testing confirmed anti-PL-7 antibodies (Figure 5).

In the context of his clinical features and anti-PL-7 positivity, a diagnosis of lung dominant anti-synthetase syndrome (ASyS) was made. The patient was commenced on prednisolone 20mg once daily, with co-trimoxazole prophylaxis against opportunistic infection and referred for assessment for ambulatory oxygen therapy, pending haematological review.

Dr Rachel Protheroe, Haematology Consultant

Bone marrow biopsy demonstrated dysplastic megakaryocytes and erythrocytes, reduced granulopoiesis and myeloid blasts (6%), consistent with a diagnosis of myelodysplastic syndrome (MDS) with excess blasts.

Myelodysplastic syndromes are clonal haematopoietic stem cell disorders characterized by dysplastic, ineffective haematopoiesis associated with progression to acute myeloid leukaemia (AML). Treatment is indicated according to the International Prognostic Scoring System (IPSS)¹; in this case, intermediate-2 risk. Such higher risk MDS carry a major risk of transformation to AML and in fit patients can be treated with intensive chemotherapy consolidated with allogeneic stem cell transplantation, but the severity of the ILD precluded this. He was therefore treated with azacitidine, a hypomethylating agent.

There is a recognised association between MDS and autoimmune phenomena (AIP), with a variety of serological and clinical syndromes of autoimmunity reported in patients with MDS. Given the temporal relationship between the development of MDS and ASyS-associated ILD, it was felt that the two may be linked.

AC

After 5 cycles of azacitabine a good response in the peripheral blood count was seen (Hb 88, WCC 1.52, Platelets 227). Unfortunately, lung function continued to deteriorate (Figure 2) with worsening dyspnoea. HRCT showed progression of the ground glass component of the ILD (Figure 4). Mycophenolate Mofetil 500mg once daily was commenced, but had to be stopped after 4 doses due to fall in neutrophils to $0.17 \times 10^9/L$. A further trial of prednisolone at a higher dose of 30mg was started without significant benefit. In view of the progressive disease despite maximum tolerable immunosuppressive therapy, a pathway of low dose prednisolone, alongside best supportive care was adopted.

AC, HG, HP, SB

We present a case of ASyS-associated ILD with a synchronous diagnosis of MDS; the simultaneous presentation suggesting a causative relationship. To the authors' knowledge, this is the first described case of ASyS developing in MDS, and of a CTD-ILD associated with MDS.

ASyS is a distinct subset of autoimmune connective tissue disease, which is historically described within the idiopathic inflammatory myopathy spectrum². It is characterised by the presence of autoantibodies against one of several cytoplasmic aminoacyl transfer RNA (tRNA) synthetase enzymes². It is most frequently associated with anti-Jo-1, although seven other autoantibodies, including anti-PL-7, have been identified³. Clinical presentation may phenotypically overlap with dermatomyositis (DM) or polymyositis (PM) but ASyS can exist in an amyopathic form⁴. Other clinical features include inflammatory arthritis, myositis, mechanics' hands, fever, and Raynaud's. Associated ILD is common, with lung involvement present in 50-90% cases depending on the autoantibody expressed⁵. In published studies of anti-PL-7 associated ASyS, pulmonary involvement occurred in 66-100%^{3,6}. The most common pattern of lung involvement is NSIP, with organising pneumonia (OP) occurring in a minority of cases⁶.

Management of ASyS-associated ILD involves pharmacological and non-pharmacological measures. As in other chronic respiratory conditions, oxygen therapy, vaccination and smoking cessation should be addressed. Pulmonary rehabilitation should be encouraged for patients with myositis-associated ILD; studies have demonstrated that physical exercise is safe in myositis and improves muscle strength⁷, although rehabilitation programmes should be delayed if there is evidence of active muscle inflammation. Immunomodulatory agents form the mainstay of pharmacological treatment of ASyS-ILD. No specific guidelines exist, and the approach should be tailored to the acuteness and severity of the initial presentation. A proposed algorithm was published recently⁸, which suggested that in patients with stable mild-moderate disease, oral prednisolone should be started alongside a steroid-sparing agent (Mycophenolate Mofetil or azathioprine). If there is improvement or stabilisation, the steroid can be weaned down. In patients presenting acutely or in respiratory compromise, high dose steroids (typically pulsed intravenous methylprednisolone) should be started in combination with cyclosporin or a calcineurin inhibitor. Rituximab, an anti-CD20 monoclonal antibody, has been used in refractory cases with some success⁹. The proposal suggests that in treatment failure, a trial of intravenous immunoglobulin or referral for transplantation is considered.

There is a recognised association between MDS and autoimmune phenomena (AIP). A recent large-scale multi-centre study of 1,408 patients with MDS found evidence of an autoimmune process in 28%¹⁰, in keeping with previous studies. In this cohort, the presence of AIPs was associated with improved overall survival (60 months vs 45 months), and a lower chance of transformation to acute leukaemia (23% vs 30%). A wide range of autoimmune phenomena have been reported in MDS, with systemic conditions such as Sjogrens syndrome, systemic lupus erythematosus and systemic vasculitides all described. Serological evidence of autoimmunity is also frequently identified¹¹. The underlying pathogenic mechanisms are unknown, although deranged cytokine production, as well as more specific changes in T-cell responses to antigen presentation and abnormal B-cell and T-cell interactions have been proposed. In published series, immunosuppressive therapy has improved the AIP and haematological indices in a proportion of cases, but this effect is not consistent¹².

A distinct association between ILD and MDS has also been described. In a cohort study of 827 MDS patients, 2% had ILD, a rate significantly higher than that of the general population¹³. In this study, only one of the 18 patients with ILD had a CTD diagnosis (rheumatoid arthritis), and none had received a hypomethylating agent prior to diagnosis of ILD. Telomere dysfunction was proposed as a potential shared mechanism but further research is required to elucidate the exact pathophysiology.

This case describes a lung-dominant ASyS developing in the context of MDS, presenting with ILD and bone marrow failure. An important alternative diagnosis to consider in the combination of bone marrow failure and lung fibrosis is telomere-related disease. Telomeres are highly conserved 5'-TTAGGG-3' repeats at the ends of chromosomes that confer protection during cellular replication. At a molecular level, telomere dysfunction triggers a DNA damage response cascade, that results in cellular senescence and apoptosis that may be cell- or tissue-type- specific. The clinical manifestations of telomere-mediated disease are thus diverse, although the triad of bone marrow failure, liver cirrhosis and idiopathic pulmonary fibrosis is considered to be highly predictive of germline telomere mutation¹⁴. Six telomere-related genes have been linked to the development of familial pulmonary fibrosis, although TERT (Telomerase reverse transcriptase) mutations are most frequent, occurring in approximately 15% of those with affected kindreds¹⁵. If suspected, telomere length analysis or genetic analysis of telomerase-related genes (TERT, TERC, DKC1, TINF2, PARN and RTEL1) could be performed.

This case raises several important points for clinicians. ILD is a feature of many CTDs, and as in this amyopathic presentation, the classic musculoskeletal features of the condition may be subtle or absent. New ILD presentations should therefore prompt a thorough evaluation for symptoms and signs of a CTD. As a minimum we suggest this should include a detailed history exploring arthralgia, myalgia, skin changes and presence of Raynaud's or sicca symptoms, with careful examination of the hands for subtle clinical signs of mechanic hands, fingertip ulceration, rugged cuticles, dilated nailfold capillaries, finger tapering, Gottron's papules and heliotrope rashes of the face, posterior neck and shoulders (shawl sign) or of the anterior neck and chest (V-sign). A basic laboratory screen of ANA, rheumatoid factor, anti-CCP (cyclic citrullinated peptide) and creatinine kinase (CK) is recommended. In context of suspected anti-synthetase syndrome, a negative ANA screen does not necessarily indicate autoantibody negativity; the presence of cytoplasmic staining using cell immunofluorescence would be characteristic. We suggest full immunoblot for myositis specific antibodies (Anti: Jo-1, PL-12, PL-7, KS, OJ, EJ, ZO, Ha and MDA-5) and myositis associated antibodies in those with muscle complaints, unexplained elevated CK or clinical signs such as mechanic hands. Secondly, given the recognized association between MDS and ILD and autoimmune conditions, the presence of an unexplained cytopenia should prompt referral to a haematologist. Finally, this case demonstrates the complex, multi-systemic nature of CTD-ILD, requiring the input of respiratory and rheumatology physicians with MDT support. A specialist combined Respiratory/Rheumatology ILD-CTD clinic, such as that run at our centre, helps to streamline this process.

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